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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/024,648	12/19/2001	Heather J. Belmont	49663(48340)	2636

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
03/31/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/024,648	BELMONT ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-7,30,31,38,39,41-45,47 and 112-118* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4-7, 30-31, 38-39, 41-45, 47, and 112-118* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response received on 11/2/09 has been entered. No claims have been added, canceled or amended with the instant response. Claims 3, 8-29, 32-37, 40, 46, and 48-111 have been previously canceled. Claims 1-2, 4-7, 30-31, 38-39, 41-45, 47, and 112-118 are pending and currently under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in a previous office action.

It is again noted that claims 1-2, 4-7, 30-31, 38-39, 41-45, 47, and 112-118 continue to read broadly on any non-human transgenic animal. The claims have been and continue to be examined in view of the elected subject matter, i.e. a transgenic mouse. It is further noted that the species of mouse was elected **without** traverse, and that neither the elected species nor the generic claims are found to be allowable.

Claim Rejections - 35 USC § 103

The rejection of claims 1-2, 4-7, 30-31, 38-39, 41-47, 112-113, and 116-118 under 35 U.S.C. 103(a) as being unpatentable over U.S. 5,859,312 (1/12/99), hereafter referred to as Littman et al. in view of Mombaerts et al. (1993) Cell, Vol. 75, 275-282, McMurry et al. (1997) Mol. Cell. Biol., Vol. 17 (8), 4553-4561, Rowen et al. (1996) Science, Vol. 272, 1755-1762, and Rack et al. (1997) Blood, Vol. 90(3), 1233-1240, is maintained. Applicant's arguments have

been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

Applicant's response provides no arguments concerning the teachings of Littman et al., Mombaerts et al., Rowen et al. and Rack et al., and instead focuses completely on the teachings of McMurry et al. The applicant is reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Further, the applicant has previously presented similar arguments concerning McMurry et al., which hinge entirely on speculation as to what the authors of McMurry et al. intended when they designed the human TCR delta locus to include a mutation which would allow for productive rearrangement of the transgene, but not the expression of functional human TCR delta protein. While the Office will continue to respond to these arguments, see below, it may be worthwhile at this point in prosecution to revisit what the claims under examination actually recite. Applicant's arguments concerning McMurry et al. repeatedly try to make the point that the authors were concerned that the expression of functional human TCR delta protein would influence thymic development and alter normal T cell development. While these allegations are addressed specifically below, the applicant is reminded that the claims as written contain no limitations regarding "normal" T cell development, thymic development etc. The claims as written, aside from setting forth the structural limitations of the non-human transgenic animal, simply state that the transgenic animal is "..capable of productive rearrangement of the human T-cell receptor alpha and beta loci to encode functional heterologous T-cell receptors" (claims 1, 2, 4, 30-31, 38-39, 41-45, 47, and 112). Claims 5-6

further recite that the heterologous TCR are expressed, and claim 7 recites that the animal is capable of producing an immune response to antigen comprising T cells which comprise a human T-cell receptor. Claim 113 is similar to claim 6. Claim 116 further recites that the animal is capable of producing a repertoire of functional heterologous TCRs, and claims 117-118 depend on claim 5 and further recite that the heterologous TCRs are "necessary for T-cell development, T cell maturation or antigen stimulated responses" (claim 117). Thus, the only functional limitation in the majority of the claims as written is that the transgenic animal is capable of productively rearranging the human T-cell receptor alpha and beta loci to encode functional heterologous T-cell receptors. It is further noted that while claims 117-118 do refer to T cell development and maturation, the claims simply state that either the expression of the heterologous TCR is necessary for T cell development or maturation (claim 117) or to "effect T cell development" (claim 118). However, there are no limitations in any of these claims, including claim 117-118 that the transgenic non-human animal exhibit "normal" T cell development or maturation, or "normal" thymic development. Thus, a *prima facie* case of obviousness over the instant claims does not require teachings and motivation to restore or produce "normal" thymic or T cell development. All that is required for the majority of the claims is teaching, motivation, and a reasonable expectation of success in making a transgenic non-human animal which has inactivated endogenous TCR loci, comprises unrearranged human TCR beta and alpha loci, and is capable of productively rearranging the human loci to encode functional alpha and beta proteins. For claims 5-7 and 113, additional reasonable expectation is required for the expression of functional TCR, and for claims 117-118, a reasonable expectation that the human TCR could participate in T cell development and maturation. It is maintained that

the combined teachings of Littman et al., Mombaerts et al., McMurry et al., Rowen et al., and Rack et al. provide just such teachings, motivation, and reasonable expectation of success. As noted in previous office actions, obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See *In re O'Farrell,* 7 USPQ2d 1673 (CAFC 1988).

Turning to the arguments provided with the instant response, the applicant again argues that the constructs taught by McMurry et al. were designed with mutated V gene segments such that the rearranged TCR transgene does not express functional TCR protein products because the authors of McMurry et al. were concerned that a productively rearranged human TCR would interfere with normal T cell development. The applicant refers again to the teachings of Lauzurica and Krangel June 1994, of record and discussed in detail in previous office action, which in applicant's opinion show that the mutation was introduced into the human TCR delta loci to prevent the expression of functional transgene which would influence thymic development, and further cites Roberts et al., made of record in the instant response, for stating that the mutation was introduced because expression of a functional TCR could alter T cell development. The applicant states that these references show that the defective loci was used to prevent the functional TCR protein from influencing thymic development and altering normal T cell development. As discussed in detail above, this line of argument is irrelevant to the question of obviousness of the instant claims under examination. The applicant is in effect arguing limitations not present in the claims as written. Further, the office has explained repeatedly that McMurry et al. was only cited for providing evidence that an unrearranged human TCR loci transgene can successfully undergo rearrangement in a transgenic mouse. Whether or not thymic

development/T cell development in a transgenic mouse with inactivated endogenous TCR loci and comprising unrearranged human alpha and beta TCR loci transgenes would proceed identically to that seen "normally" in a human or a wild type mouse is irrelevant to the determination of obviousness of the instant claims as written which contain no functional limitations regarding "normal" T cell or thymic development.

However, for the sake of making a complete response to applicant's arguments, the office once again reiterates that the original Lauzurica and Krangel publication in 1994, which gives the first description of the transgenic mice comprising a human TCR delta locus used by McMurry, specifically states the reason why the mutations to the V gene segments in the construct were added. On page 45, under the heading "strategy", the authors state, "[w]e wanted the construct to serve as an innocuous reporter that would not influence the rearrangement of endogenous TCR genes via the process of allelic exclusion" (Lauzurica and Krangel (January, 1994), J. Exp. Med., Vol. 179, 43-55- page 45). Applicant's statement that Sleckman et al. (of record), published years later, teaches that productive rearrangement of one TCR delta allele does not inhibit rearrangement of the other TCR delta allele and that therefore it is not clear why McMurry would expect or predict that expression of a rearranged TCR delta would affect allelic exclusion of endogenous TCR loci, is disingenuous since Sleckman et al. specifically states in their abstract that before the findings of Sleckman et al. were published in 1998, it was not known whether assembly of TCR delta variable region genes was regulated in the context of allelic exclusion. Thus, back in 1994, or even in 1997 when McMurry et al. was published, the authors Lauzurica and Krangel did not know whether the rearrangement and expression of a human TCR would affect allelic exclusion of endogenous TCR loci and the authors were

specifically interested in answering questions concerning rearrangement and lineage commitment of the endogenous mouse loci. Scientific findings made years later cannot change the specific teachings of the original paper describing the strategy for making the transgenic mice used in McMurry as cited above.

Regarding applicant's contention that single statements taken from the later Lauzurica and Krangel publication and Roberts et al. show that the authors of McMurry et al. were concerned about the effects of expression of a human TCR delta on normal T cell development, it is reiterated that the claims as written contain no limitation that the transgenic mice exhibit "normal" T cell development, and there is simply no teachings in any of the cited references including McMurry et al. that mouse T cells expressing a human TCR delta chain would fail to develop, pass through selection in thymus, and recognize antigen in the periphery. Thus, this line of argument by applicant is based on limitations not present in the claims as written and is not found persuasive in demonstrating that a skilled artisan at the time of filing would not have had a reasonable expectation that a transgenic mouse comprising unrearranged human TCR alpha and beta loci would be capable of expressing functionally rearranged human TCR, or that such T cells expressing such human TCR would be capable of recognizing and responding to antigen.

In regards to the teachings of Rothe et al .and Viney et al., these references originally cited in applicant's IDS of 5/16/05, were referred to by the examiner to refute applicant's continued argument in the previous response that the skilled artisan would not have predicted that a mouse T cells expressing a productively rearranged human TCR would develop normally in the mouse. The applicant now argues that in their opinion neither reference shows the response of human TCR in transgenic mice to antigen in the context of MHC and that Rothe et al

.teaches that expression of human TCR beta chain from a rearranged TCR beta chain transgene in transgenic mice affects the number and phenotype of T cells in the thymus. The applicant also provides the post-filing reference Lacorazza et al. which shows that the introduction or rearranged TCR alpha and beta transgenes into a mouse affects early thymocyte development. In response, the point of citing Rothe et al. was to show that contrary to applicant's prior arguments, the skilled artisan at the time of filing would have had a reasonable expectation that mouse T cells expressing human TCR chains would be capable of developing into functional T cells. As for the form of antigen used in Rothe et al., note that the alloantigens used in Rothe et al. are in fact a form of antigen and there are no limitations in the claims regarding the responses to MHC restricted antigens. As for Lacorazza et al,. as a post-filing reference, Lacorazza et al. cannot be relied upon to demonstrate the state of the art at the time of filing. However, it is noted that Lacorazza et al. states that the effects on development are due to the premature expression of the transgenic TCR which does not have to undergo rearrangement, a different scenario from that claimed. Finally, as discussed in detail above, applicant's focus on McMurry et al., references cited by McMurry et al., and other evidentiary publications cited by applicants or by the examiner as rebuttal evidence, ignores the fact that the rejection of record is based on the combined teachings of Littman et al. in view of Mombaerts et al., McMurry et al., Rowen et al. and Rack et al., and is further predicated on limitations concerning normal T cell development which are not part of the claims as written.

Therefore, for reasons of record and the discussion above, the rejection stands.

The rejection of claims 114-115 under 35 U.S.C. 103(a) as being unpatentable over U.S. 5,859,312 (1/12/99), hereafter referred to as Littman et al. in view of Mombaerts et al. (1993) Cell, Vol. 75, 275-282, McMurry et al. (1997) Mol. Cell. Biol., Vol. 17 (8), 4553-4561, Rowen et al. (1996) Science, Vol. 272, 1755-1762, and Rack et al. (1997) Blood, Vol. 90(3), 1233-1240 as applied to claims 1-2, 4-7, 30-31, 38-39, 41-47, 112-113, and 116-118 above, and further in view of the NCBI database is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed below.

The applicant argues that the NCBI Accession Number NG_001332 referred to by the examiner was not used until 2002, after the effective filing date of the instant application and has provided a copy of the revision history for this accession number printed from the NCBI website. In response, while the Accession Number currently being used by the NCBI was apparently introduced in 2002, the actual sequence of the entire human alpha TCR loci was still present in the publicly accessible NCBI database prior to the time of filing. The applicant is already on record admitting this sequence was available in the NCBI database. Page 44 of the specification clearly states in lines 9-12, "The human TCRα locus is located on chromosome 14q11.2 and has been sequenced in its entirety and deposited into the National Center for Biotechnology Information (NCBI) nucleotide database". Therefore, while the Accession number for this sequence has changed, the evidence of record clearly shows that the publicly available NCBI nucleotide database did contain this sequence at the time of filing. As such, the rejection of record is maintained.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, the technology center fax number is (571) 273-8300. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the

USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633